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This research supported by the Office of Naval Research was focussed on how memories for the learning of skilled sensory-motor behaviors are learned, where they are stored in the brain and how these discoveries inform computational models of learning and information processing. We were able to show that 1) these memories are formed and stored in the cerebellum and 2) that the cerebellar neural networks provide a most useful framework for computational modeling.

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THE CEREBELLUM AND SENSORY-MOTOR CONDITIONING

Classical conditioning is a valuable paradigm for analysis of the brain substrates of sensory-motor learning because of the high degree of experimental control possible. In a typical conditioning experiment, a previously neutral conditioned stimulus (CS) is repeatedly paired with a response-evoking stimulus called the unconditioned stimulus (US). Eventually, the CS may come to evoke a conditioned response (CR) similar to that evoked by the US. The time between CS onset and US onset is defined as the interstimulus interval (ISI). By varying the ISI and the intensity, duration, number and type of stimuli, a large number of conditioning phenomena can be elicited.

We employed this general paradigm using classical conditioning of the rabbit eyeblink/nictitating membrane response as a model system to analyze brain substrates of basic associative learning. Our goals were threefold: 1) To localize the sites of memory formation and storage, 2) to identify the entire essential circuitry for this basic form of associative memory, and 3) to make use of this knowledge to develop computational systems that analyze, code, store, retrieve and evaluate signals. In the latter goal our hope was that by making use of biological

principles, i.e. how the brain processes information, we could improve on current computational procedures. We achieved all three goals in the course of this project.

The rabbit eyeblink preparation has proven particularly useful for classical conditioning studies because of low background response rates (see Gormezano, Kehoe & Marshall, 1983, for review). In this preparation, the rabbit is restrained in a plexiglass box during the presentation of stimuli. Most commonly, the US is a corneal airpuff or paraorbital shock which evokes protective closure of the eyelid and extension of the nictitating membrane, or third eyelid. The CS may be a light, a tone or a tactile stimulus, which comes to evoke a blink CR. This preparation does not exhibit sensitization pseudoconditioning with normal stimulus and training parameters. Although our focus in this paper is on the critical cerebellar circuitry in classical conditioning, it is well to keep in mind that other structures may be critically required to account for the full range of phenomena observed in the normal intact animal. Other brain structures, particularly the hippocampus, can play critical roles when conditioning task demands are appropriate (c.f., Akase et al., 1989; Berger & Thompson, 1978; Moyer et al., 1990; Solomon et al, 1986b). Furthermore, there is also a fear learning system involving the amygdala, which is engaged if the US is sufficiently aversive (Hitchcock & Davis, 1986; LeDoux et al., 1990; Powell, Lipkin & Milligan, 1974; Wagner & Brandon, 1989). Therefore, a model of the cerebellar substrates of conditioning should not be expected to account for all aspects of conditioning behaviors. Interestingly, the cerebellum does appear necessary in certain forms of instrumental avoidance learning.

Cerebellar System Essential for Simple (Delay) Classical Conditioning of Discrete Responses.

Due in large part to its extraordinary anatomical organization, the cerebellum has long been a favored structure for modeling a neuronal learning system, dating from the classic papers of Marr (1969) and Albus (1971). Our empirical work to date has been guided by these models and the related views of Eccles (1977) and Ito (1984) and our results constitute a remarkable verification of the spirit of these theories.

First, a word about the organization of the cerebellar system. As indicated in the highly simplified schematic block diagram of Figure 1, there are two major projection systems to the cerebellum. The mossy fibers project from the pontine nuclei and other sources to the cerebellar nuclei (e.g., interpositus) and cortex and convey all varieties of sensory information to the cerebellum. The other system projects from a structure termed the inferior olive, which in term is preferentially activated by higher threshold somato-sensory (i.e. nociceptive) projections. Inferior olivary neurons project to the cerebellar nuclei and cortex as climbing fibers. The only efferent projection from the cerebellum to other brain structures are from the cerebellar nuclei, here the interpositus. A major efferent target is the red nucleus, which in turn projects to premotor and motor nuclei in the brainstem and spinal cord.

The granule cells in cerebellar cortex are activated by mossy fiber projections. The granule cells in turn give rise to the parallel fibers that form excitatory synapses en passage with Purkinje neuron dendrites. There are about 100,000 parallel fiber synapses on each Purkinje neuron! The climbing fibers from the inferior olive, in striking contrast, have a one-to-one connection to Purkinje neurons where they form powerful excitatory synapses. (There are also several types of inhibitory interneurons in cerebellar cortex.) It is partly the extraordinary differences in the two

projection systems that has fascinated theorists. (The cerebellar cortex is everywhere the same in its anatomical structure, unlike the cerebral cortex that has specialized sensory, motor and association areas.) The only output from the cerebellar cortex is from the Purkinje neurons. They project only to cerebellar and vestibular nuclei and their synaptic actions are purely inhibitory (GABA mediated). To greatly oversimplify the classical theories of Marr and Albus, the mossy-granule-parallel fiber system conveys detailed information of movements and contexts and the climbing fiber system conveys "error" information. Recall that both mossy and climbing fiber systems project to the cerebellar nuclei (interpositus) and the nuclei project excitatory information to other brain structures. So the cerebellar cortex forms a higher-order loop that exerts inhibitory modulation on the nuclei.

The block diagram of Figure 1 also serves to summarize our overall empirical results to date and is a much simplified version of our current qualitative working model of the role of the cerebellum in basic delay classical conditioning of discrete responses. (Laterality is not shown; the critical region of the cerebellum is ipsilateral to the trained eye (or limb), the critical regions of the pontine nuclei, red nucleus and inferior olive are contralateral.) Unless otherwise noted, in this section the data all refer to the basic delay eyeblink CR (tone CS 350 msec, coterminating with 100 msec corneal airpuff US). We review our previous work very briefly here.

The CR Pathway

We first showed that neurons in the interpositus nucleus respond to the CS and US and develop an amplitude-time course "model" of the learned behavioral response that precedes and predicts the occurrence and form of the CR within trials and over the trials of training (McCormick et al., 1982a; 1984a,b; Foy et al., 1984), a result that has been repeatedly replicated (e.g., Berthier

& Moore, 1990; Steinmetz, 1990b; Tracy et al., 1991). Electrical stimulation in this region of the interpositus elicits eyeblink responses in naive animals; the circuit is hard-wired from interpositus to behavior (Chapman et al., 1988). We first showed that lesions of the interpositus abolished the CR and had no effect on the UR (McCormick et al., 1982a). This result has been replicated in approximately 15 subsequent studies (see, e.g., Clark et al., 1984; Lavond et al., 1985; Steinmetz et al., 1989, 1992; Thompson, 1990; Yeo et al., 1985a). Similarly, lesions of the superior cerebellar peduncle and red nucleus can abolish the CR (Haley et al, 1988; McCormick et al., 1982b; Rosenfeld et al., 1985; Rosenfeld & Moore, 1983).

Appropriate cerebellar lesions in humans completely prevent learning of the eyeblink CR and have no effect on the UR (Daum et al., 1993; Lye et al., 1988; Solomon et al., 1989b). The possibility that effective interpositus lesions abolish the CR by small effects on the UR (the "performance" argument, i.e. Welsh & Harvey, 1989) has been decisively ruled out in a series of studies (Disterhoft et al., 1985; Ivkovich et al., 1993; Logan, 1991; Steinmetz et al., 1992; Yeo, 1991). The argument was that if the CS and the US are made equivalent as response eliciting stimuli, then the effect of the interpositus lesion would be similar on both the CR and the UR. We trained animals with a very weak US just suprathreshold for learning (Ivkovich et al., 1993). The CR and the UR were comparable in amplitude before lesion. Following lesion the CR was completely and permanently abolished but the UR was unchanged.

The US Pathway

Lesions of the critical region of the inferior olive, the face representation in the dorsal accessory olive (DAO), completely prevent learning if made before training and result in extinction/abolition of the CR if made after training (McCormick et al., 1985; Mintz et al., 1988;

Voneida et al., 1990 (limb flexion); Yeo et al., 1988). Unit activity in this critical DAO region does not respond to the CS, responds only to US onset, shows no learning-related activity, and decreases as animals learn (Sears & Steinmetz, 1991a). Electrical microstimulation of this region serves as a very effective US (Mauk et al., 1986; Steinmetz et al., 1989; Thompson, 1989) as does stimulation of cerebellar white matter (Swain et al., 1992). All these data argue that the DAO-climbing fiber system is the essential US reinforcing or "teaching" pathway for the learning of discrete responses. To our knowledge, this is the only system in the brain, other than reflex afferents, where the exact response elicited by electrical stimulation can be conditioned to any neutral stimulus. Current evidence suggests that this system plays a key role in the neural instantiation of the error correcting algorithm in classical conditioning. We elaborate this below.

The CS Pathway

Electrical stimulation of the pontine nuclei (sending mossy fiber projections to cerebellar cortex and interpositus -- Milhailoff, 1993; Shinoda et al., 1992; Steinmetz & Sengelaub, 1992; J. Thompson et al., 1985, 1991) serves as a supernormal CS and lesions and recording evidence argues very strongly that this is the essential CS pathway in classical conditioning of discrete response (Knowlton & Thompson, 1988; Lewis et al., 1987; Solomon et al., 1986a; Steinmetz, 1990a,b; Steinmetz et al., 1986, 1987, 1989; Tracy et al., 1992).

Purkinje Neuron Activity

Many Purkinje neurons in cerebellar cortex, particularly in HVI, are responsive to the tone CS and the corneal airpuff US in naive animals. Before training, the majority of Purkinje neurons that are responsive to the tone show variable increases in simple spike discharge frequency in the CS period. (Simple spikes are evoked in Purkinje neurons by the parallel fiber axons from granule

cells in cerebellar cortex, activated in turn by mossy fiber projections, the CS pathway noted above.) After training, the majority show learning-induced decreases in simple spike frequency in the CS period; a result consistent with a process of long-term depression (LTD) as a mechanism of memory storage in the cerebellum (Ito, 1994; Linden & Connor, 1995). However, a significant minority show the opposite effect (Berthier & Moore, 1986; Donegan et al., 1985; Foy & Thompson, 1986; Thompson, 1986). Before training, Purkinje neurons that are influenced by the corneal airpuff consistently shows an evoked complex spike to US onset (complex spikes are evoked in Purkinje neurons by climbing fibers from inferior olive neurons). In trained animals, this US evoked complex spike is virtually absent on paired CS-US trials when the animal gives a CR but present and normal on US alone test trials (Foy & Thompson, 1986; Thompson, 1990; Krupa et al., 1981) (see US Pathway, above).

Reversible Inactivation

As we noted, the diagram of Figure 1 shows in highly simplified schematic form the essential memory trace circuit for classical conditioning of discrete responses, based on the lesion, recording and stimulation evidence described above. Interneuron circuits are not shown, only net excitatory or inhibitory actions of projection pathways. Other pathways, known and unknown, may also of course be involved. Many uncertainties still exist, e.g., concerning details of sensory-specific patterns of projection to pontine nuclei and cerebellum (CS pathways), details of red nucleus projections to premotor and motor nuclei (CR pathway) and the relative roles of the cerebellar cortex and interpositus nucleus.

We and our associates have recently developed a new approach to localize sites of neuronal plasticity in learning ("memory traces") using methods of reversible inactivation (drugs, cooling).[1]

Inactivation procedures, per se, are of course not new but because we have identified the essential (necessary and sufficient) circuitry for classical conditioning of eyeblink and other discrete responses (e.g., limb flexion, head turn, etc.) we can apply the method effectively. Considering brain regions and pathways that are necessary for performance of the CR (shaded and labeled regions in Fig. 1), i.e. where inactivation completely prevents performance of the CR, we inactivated each region in separate groups of animals while the animals were being trained. If inactivation of a region prevents learning, then the memory must be formed at or beyond this region in the circuit. If inactivation of a region does not prevent learning, then the memory must be formed before this region in the circuit.

Several parts of the circuit have been reversibly inactivated for the duration of training (eyeblink conditioning) in naive animals, indicated by shadings labeled a, b, c, d and encircled e in Figure 1. The motor nuclei essential for generating the UR and CR (primarily 7th and accessory 6th) were inactivated by infusion of muscimol (6 days) or cooling (5 days) during standard tone-airpuff training (a in Fig. 1) (J. Thompson, Krupa, Weng, & Thompson,, 1993; Krupa, Weng & Thompson, in press; Zhang & Lavond, 1991). The animals showed no CRs and no URs during this inactivation training; indeed they showed no behavior at all -- performance was completely abolished. However, the animals exhibited asymptotic CR performance and normal UR performance from the very beginning of post-inactivation training. Thus, performance of the CR and UR are completely unnecessary for normal learning and the motor nuclei make no contribution to formation of the memory trace -- they are efferent from the trace.

Inactivation of the magnocellular red nucleus is indicated by b in Fig. 1. Inactivation by low doses of muscimol for six days of training had no effect on the UR but completely prevented

expression of the CR (Krupa et al., 1993). Yet animals showed asymptotic learned performance of the CR from the beginning of post-inactivation training. Training during cooling of the magnocellular red nucleus gave identical results -- animals learned during cooling, as evidenced in post-inactivation training, but did not express CRs at all during inactivation training (Clark & Lavond, 1993). However, cooling did significantly impair performance of the UR (but the animals learned normally), yet another line of evidence against the "performance" argument, (see above). Consequently, the red nucleus must be efferent from the memory trace.

Inactivation of the dorsal anterior interpositus and overlying cortex (c in Fig. 1) by low doses of muscimol (6 days), by lidocaine (3 days, 6 days), and by cooling (5 days) resulted in no expression of CRs during inactivation training and no evidence of any learning at all having occurred during inactivation training (Clark et al., 1992; Krupa et al., 1993; Nordholm et al., 1993). In subsequent post-inactivation training, animals learned normally as though completely naive; they showed no savings at all relative to non-inactivated control animals. None of the methods of interpositus inactivation had any effect at all on performance of the UR on US alone trials. The distribution of [^{3}H]-muscimol completely effective in preventing learning included the anterior dorsal interpositus and overlying cortex of lobule HVI, a volume approximately 2% of the total volume of the cerebellum (Krupa et al., 1993). The region of the cerebellum essential for learning this task is extremely localized.

Finally, the output from the interpositus nucleus, the efferent projections that form the superior cerebellar peduncle (scp) was inactivated by lidocaine (d) or TTX (e) during training (Krupa & Thompson, 1995). As with inactivation of the red nucleus, CR expression was completely prevented during the six days of training (URs were not effected at all). The animals

learned during inactivation training as indicated by asymptotic CR performance immediately post-inactivation. In sum, inactivation of a localized region of the anterior interpositus and overlying cerebellar cortex (c) completely prevents learning but inactivation of the output from this part of the cerebellum (d, e) does not prevent learning at all. The memory trace must be at or beyond region c but before d and e. Therefore it would seem to be in region c, a localized region of the cerebellum (see Thompson & Krupa, 1994).

The Error Correcting Algorithm

The cerebellar circuitry contains all the features necessary to account for the Rescorla-Wagner (1972) error correcting algorithm in classical conditioning (the least-mean-squares or delta rule in connectionist level cognitive models of learning and memory --Rumelhart & McClelland, 1986). We feel this is a most important contribution in relating behavioral theories of learning to brain systems and mechanisms. This basic idea grew out of empirical and modeling work in our laboratory at Stanford University in the early to mid 1980's and no one person can claim sole credit (key contributors were Nelson Donegan, Mark Gluck, Joseph Steinmetz and Richard Thompson -- see Donegan, Gluck & Thompson, 1989; Thompson, 1989; Sears & Steinmetz, 1991).

In brief, we proposed that as learning developed and the learning-induced unit activity in the interpositus grew, the direct GABA-ergic inhibitory projection from the interpositus to the inferior olive (Nelson & Magnoini, 1987; Andersson & Hesslow, 1986) would increasingly inhibit neurons in the inferior olive (see Fig. 1). This in turn would of course decrease the US activation of the IO-climbing fibers projecting to the cerebellum as learning developed (see above and Fig. 1). Recall that our evidence argues strongly that US activation of the IO-climbing fiber system projecting to the cerebellum is the essential reinforcing or teaching pathway that "teaches" the circuit what

response must be learned to the CS (the CS being any neutral stimulus, e.g., light or tone, that does not itself evoke any behavioral response). A critical prediction is that at the beginning of training, US onset will evoke complex spikes (IO-climbing fibers activation) in Purkinje neurons but that this will decrease as the animal learns. Consistent with this we found that complex spikes were reliably evoked in appropriate Purkinje neurons by US onset in naive animals but not in well-trained animals (Foy & Thompson, 1986). Sears and Steinmetz (1991) subsequently verified this result by direct recordings from neurons in the inferior olive over the course of learning (see above). The degrees to which olivary neurons showed evoked responses to US onset was an inverse function of degree of learning. As noted above, recordings from appropriate Purkinje neurons in well-trained animals showed that on US alone trials, US onset evoked complex spikes but did not evoke complex spikes in the same neurons on CS-US trials where the animals performed conditioned responses (Krupa, Weiss & Thompson, 1991).

To summarize, our schematic model, based tightly on the anatomy and physiology of the cerebellar circuitry, proposed that the error signal is the strength of IO-climbing fiber activation of cerebellar neurons, ranging from maximal at the beginning of training to zero in well-trained animals. i.e. the Rescorla-Wagner error correcting algorith. Our circuit instantiation of this algorithm can account for the phenomenon of blocking (Kanim, 1969) just as does the Rescorla-Wagner algorithm. Thus, once the animal has reached asymptotic learning to all the relevant CSs, adding one additional CS and giving additional training will not result in any associative strength accruing to the additional CS.

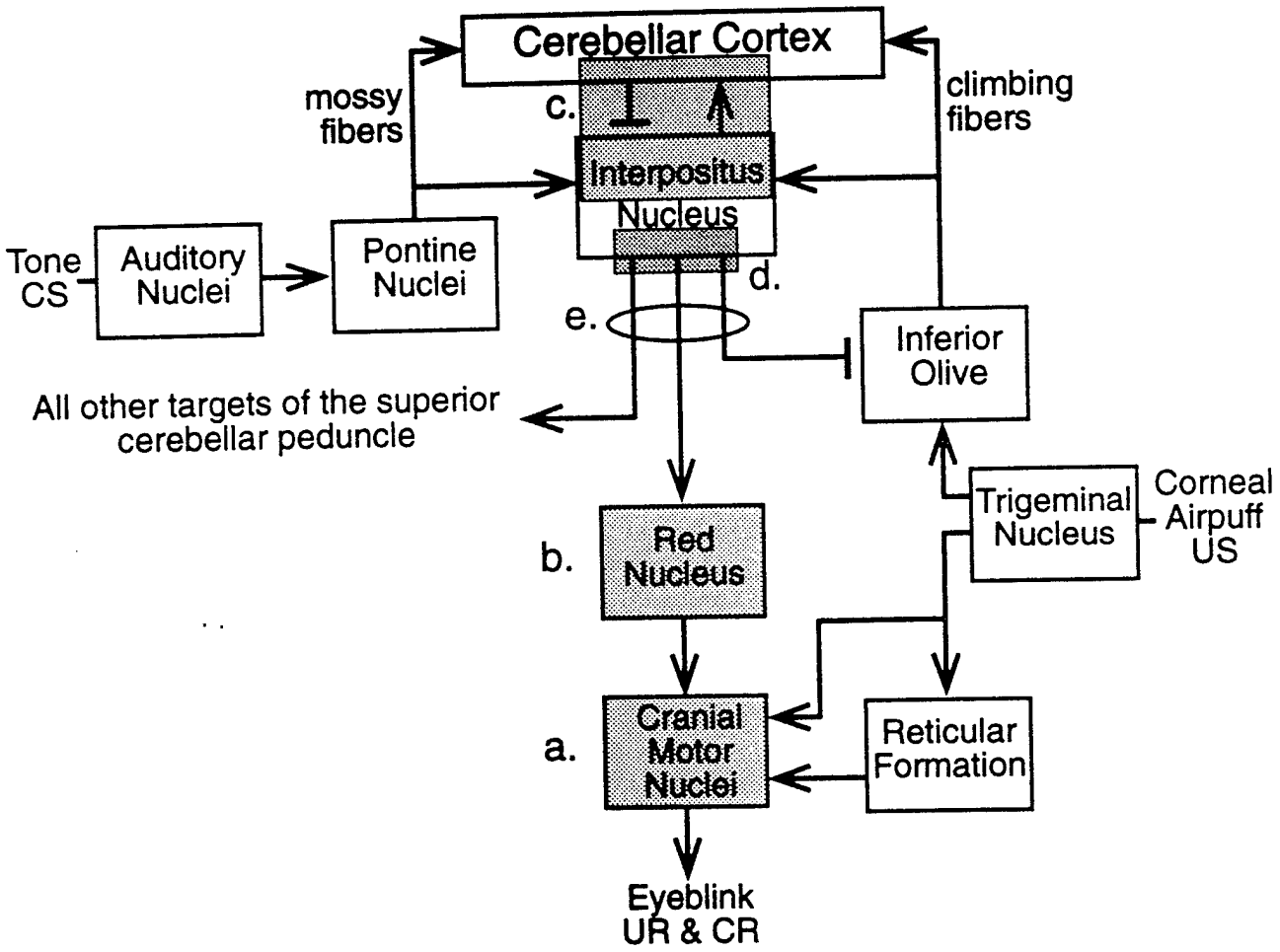
Modeling

An important aspect of our work was the development of mathematical/computational models of the neural circuits that serve to code, store and retrieve memories. Our first effort involved a connectionist level model of the four-neuron Aplysia gill-withdrawl circuit identified by Kandel and associates to exhibit the elementary properties of classical conditioning. We found that our model indeed showed some basic phenomena of learning but did not show others well, e.g. blocking (Gluck & Thompson, 1987). Using this approach we then developed connectionist models of the cerebellar neural circuit described above as the essential circuit for learning and memory of classical conditioning of discrete behavioral responses (Donegan et al., 1989; Thompson & Gluck, 1990; Gluck et al., 1991). Some interesting predictions grew out of these models, including the fact that adaptive timing of the behavioral conditioned response required feedback to the cerebellar cortex from the output of the cerebellum, a prediction that has been verified recently in empirical work (Krupa et al., 1994). Another important outcome of this modeling has been Gluck's application of the models to detect engine wear, an outcome of particular value to the Navy.

Finally, we developed a detailed physical-mathematical model of the motor neurons-muscles-movement behavior of the conditioned nictitating membrane response of the rabbit -- the so-called physical plant -- that has proved most useful in connecting our models of the cerebellar neural circuitry to the behavior (Bartha & Thompson, 1992a, b).

Figure Legend

Figure 1. Highly schematic diagram of the brain circuit essential (necessary and sufficient) for classical conditioning of discrete responses, here the conditioned eyeblink response. The shaded regions (a - d) and the circled pathway (e) were reversibly inactivated during training. See text for details.


Cerebellar Cortex
mossy fibers
climbing fibers
c.
Interpositus Nucleus
d.
e.
Tone CS
Auditory Nuclei
Pontine Nuclei
Inferior Olive
All other targets of the superior cerebellar peduncle
Trigeminal Nucleus
Corneal Airpuff US
b.
Red Nucleus
a.
Cranial Motor Nuclei
Reticular Formation
Eyeblink UR & CR

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